Metropolitan air pollution and the upper and lower airway: chronic rhinosinusitis and asthma outpatient burden

Hong-Ho Yang[1], Esther Velasquez[2], Peter H. Hwang[1]

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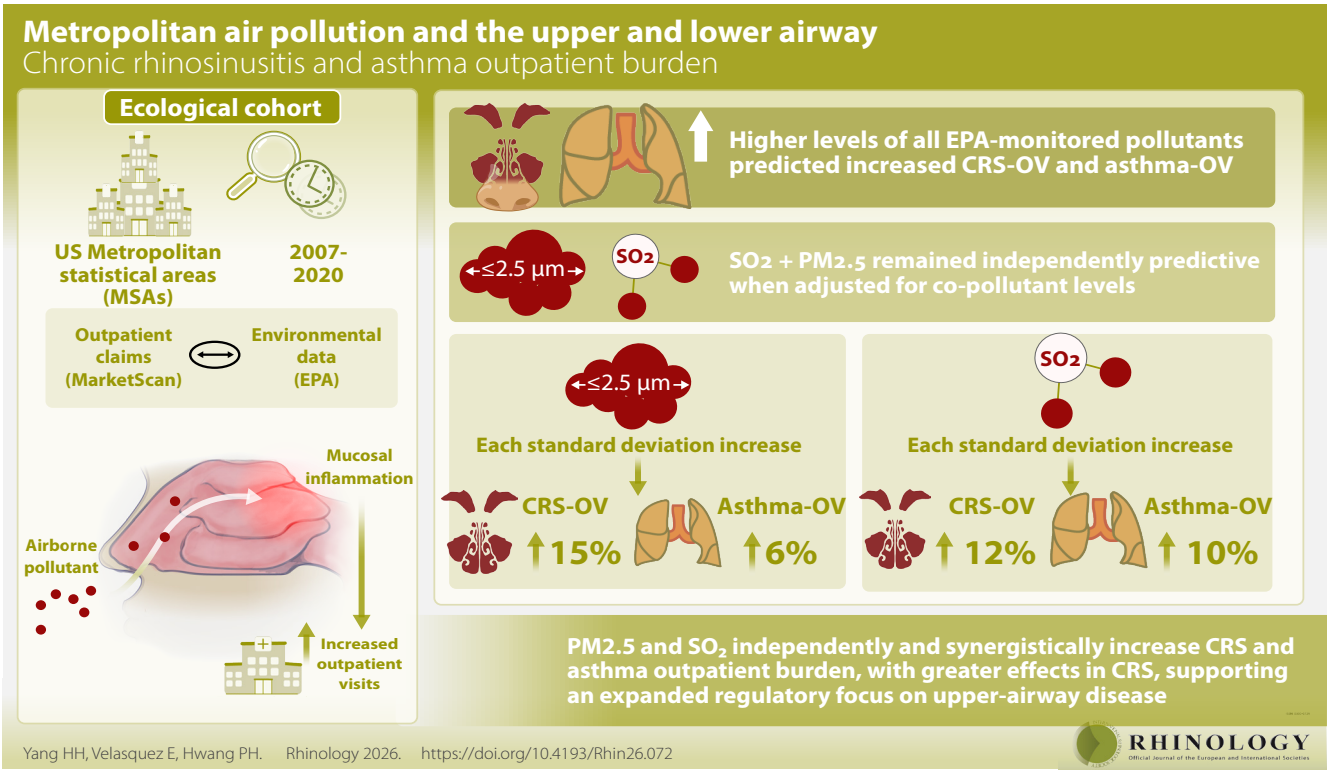

Abstract

Background: Although evidence has implicated air pollution in both upper and lower airway inflammation, regulatory efforts have primarily emphasized lower-airway outcomes. We characterize the association between ambient pollutant levels and outpatient burden of chronic rhinosinusitis (CRS) and asthma across the US. **Methodology**: We conducted an ecological cohort study of US metropolitan statistical areas (MSAs) between 2007 and 2020. Annual outpatient claims were obtained from the MarketScan database and linked with data from the Environmental Protection Agency (EPA) monitoring network. For each MSA, annual outpatient visits for CRS and asthma were normalized to the number of wellness check visits (CRS-OV, asthma-OV). Daily 365-day rolling averages were calculated for each EPA-monitored pollutants. Mixed-effects models estimated associations with CRS-OV and asthma-OV, and additive pollutant interactions. **Results**: Controlling for community health indicators, higher levels of all EPA-monitored pollutants predicted increased CRS-OV and asthma-OV. Adjusting for co-pollutant levels, PM2.5 (particles ≤2.5µm in diameter) and SO2 (gas from fossil fuel combustion) remained independently predictive. Each standard deviation increase in PM2.5 corresponded to 15% and 6% increases in CRS-OV and asthma-OV, while each standard deviation increase in SO_2 corresponded to 12% and 10%, respectively. Positive additive interaction between PM2.5 and SO2 was observed for both CRS-OV and asthma-OV. **Conclusions**: While EPA-monitored pollutants were broadly associated with outpatient burden, PM2.5 and SO2 emerged as independent and synergistic predictors after co-pollutant adjustment, with stronger associations for CRS compared to asthma. Regulatory focus should extend beyond lower-airway outcomes and include upper-airway morbidity as a critical indicator of pollution–related burden.

Key words: air pollution, airway, chronic rhinosinusitis, asthma

Introduction

Air pollution is a well-established contributor to respiratory tract pathology [1,2]. Given robust evidence supporting the association between $PM_{2.5}$ exposure and asthma exacerbations, COPD progression, and cardiopulmonary hospitalizations, national air quality standards have historically prioritized lower-airway conditions as sentinel endpoints [3-10]. In contrast, upper-airway pathologies remain underrepresented in regulatory assessments. Chronic rhinosinusitis (CRS), an upper airway condition characterized by persistent inflammation of the nasal and paranasal sinus mucosa, has been increasingly linked to air pollutant exposure [11]. Emerging evidence suggests that higher pollutant levels are associated with increased CRS incidence, greater symptom severity, and higher outpatient demand [12-21]. Yet, CRS is rarely incorporated into regulatory frameworks [5,7,8].

The Environmental Protection Agency (EPA) operates monitoring networks that generate pollutant data used to determine attainment of the National Ambient Air Quality Standards (NAAQS) [22]. Establishing quantifiable relationships between these monitored concentrations and real-world healthcare burden is essential for informing resource allocation. Moreover, given the complex interplay among ambient pollutants, evaluating their joint effects can help policymakers prioritize reductions with the greatest potential for outsized health benefits, rather than treating each pollutant in isolation [23].

In this study, we conduct a national ecological cohort analysis linking EPA multi-pollutant monitoring data with commercial outpatient claims across U.S. metropolitan statistical areas (MSAs). We aimed to characterize the associations between ambient pollutant levels and subsequent outpatient burden for CRS, accounting for potential interactions between pollutant pairs. Asthma, a lower-airway disease routinely included in air pollution regulatory frameworks, was examined in parallel as a benchmark for comparison [5,7,8,10].

Materials and methods

Data source and study design

We conducted a national ecological cohort study linking de-identified outpatient claims from the Merative™ MarketScan® Commercial Database with ambient air quality data from the U.S. EPA Air Quality System (AQS). Claims were aggregated at the MSA level, and AQS monitor data were aggregated to core-based statistical areas (CBSAs) and mapped to MSAs. The study was approved by the Stanford University Institutional Review Board (PHS 40974).

Study population and outcomes

Details of data curation are shown in Figure 1. We included outpatient claims for adults aged 18–65 years from U.S. MSAs between January 1, 2007, and April 5, 2020. CBSAs, as defined by the U.S. Office of Management and Budget, include MSAs (≥50,000 population), micropolitan areas (μSAs; 10,000–49,999), and in some cases metropolitan divisions (MDs; subdivisions of MSAs ≥2.5 million) [24]. We restricted analyses to MSAs since they are the standard geographic unit for federal environmental and health reporting, encompass the majority of outpatient care in the U.S., and are supported by the most comprehensive EPA monitoring coverage. μSAs were excluded due to sparse monitoring and low visit volumes, while MDs were excluded to avoid artificial fragmentation of large metropolitan regions.

Outpatient encounters included services delivered in physician offices, ambulatory clinics, hospital outpatient departments, emergency departments, and other outpatient settings. We excluded records with missing enrollment, diagnosis codes, age/sex, or MSA data. The remaining claims were aggregated by MSA-year to form ecological units of analysis.

Diagnoses were identified using ICD-9/10 codes for CRS (473*, *J32**), asthma (493*, *J45**), and wellness check visits (WCs; Z0000, V700). [25] For each MSA-year, we calculated the annual counts of each diagnosis and normalized them by the number of WCs to account for baseline differences in population size and healthcare utilization across MSAs. The primary outcomes were CRS and asthma outpatient visits per 1,000 WCs (CRS-OV, asthma-OV).

Ambient pollutant exposure

EPA monitoring stations report daily means for $PM_{2.5}$ (fine particulate matter ≤2.5 μm, primarily from combustion sources such as vehicle exhaust, wildfires, and industrial emissions) and PM_{10} (coarse particles ≤ 10 μm), daily 8-hour maxima for O3 (ozone, a secondary pollutant formed by sunlight-driven reactions of air pollutants) and CO (carbon monoxide, a toxic gas produced by incomplete combustion), and daily 1-hour maxima for SO_2 (sulfur dioxide, a gas emitted from fossil fuel combustion and industrial processes) and NO_2 (nitrogen dioxide, a traffic-related gaseous pollutant). Within each CBSA, same-day readings were averaged across monitors to generate daily CBSA-level concentrations. To reflect chronic airway disease processes, we prespecified a 365-day cumulative exposure metric: for each day in year Y, we averaged concentrations over the preceding 365 days, then averaged these rolling values across all days in Y to yield the MSA-year cumulative exposure. This approach generates a smoothed, triangularly weighted annual measure that emphasizes exposures during year Y while incorporating contributions from Y–1. We selected this metric because it captures long-term pollutant burden, reduces noise from short-term fluctuations, and avoids arbitrary calendar cutoffs that drive multiplicity in lag selection. As sensitivity analyses, we re-estimated associations

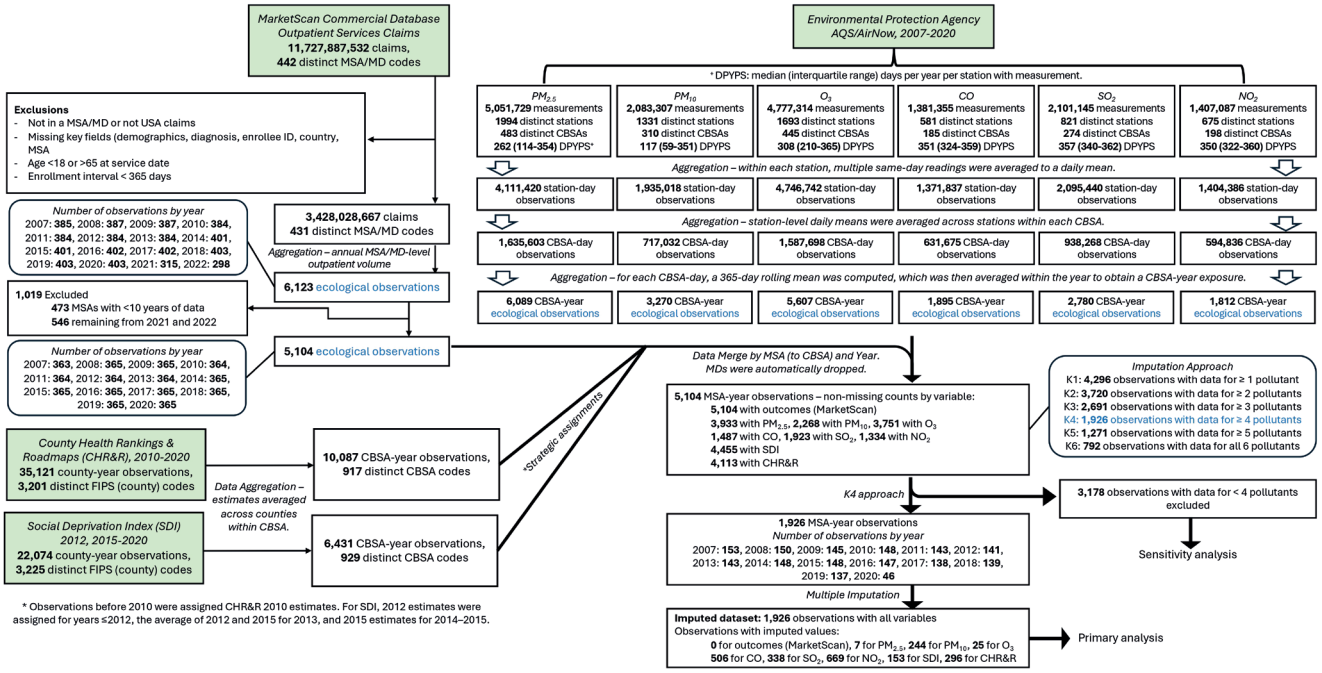

Figure 1. Data curation and aggregation workflow. Stepwise exclusions and aggregation of MarketScan outpatient claims and EPA monitoring data to the MSA/CBSA-year level, with integration of county-level social determinants (SDI, CHR&R) and multiple imputation procedures.

using Lag-0 (calendar-year mean for year Y) and Lag-1 through Lag-7 (calendar-year means up to 7 years prior) exposures. Effect estimates were directionally consistent and of similar magnitude to the cumulative metric (Figure S1).

Covariates

Covariates were selected to account for individual and area-level factors associated with healthcare seeking behavior [26]. Covariates included ecological demographics (mean age, male %), the Social Deprivation Index (SDI), and indicators from the County Health Rankings & Roadmaps (CHR&R) database. The SDI is a validated composite measure of socioeconomic disadvantage ranging from 1–100, with higher values reflecting greater deprivation [27]. CHR&R indicators included: premature mortality (years of potential life lost before age 75 per 100,000 population), fair/poor self-rated health (% adults reporting fair or poor health), poor physical-health days (mean per adult), low birthweight (% newborns <2,500 g), adult smoking prevalence (% current smokers), and adult obesity prevalence (% with BMI ≥30) [28].

Statistical methods and analytical approach

Each MSA-year was treated as an observation. We employed mixed-effects negative binomial regression with MSA random intercepts to estimate incidence rate ratios (IRRs) for CRS-OV and asthma-OV. Pollutants were modeled as continuous, standardized predictors (per-standard deviation increment) to enable comparison across pollutants. Estimates were pooled across imputations using Rubin's rules [29]. Models included unadjusted single-pollutant models (no co-pollutants, no demographic or community health covariates), unadjusted multi-pollutant models (all pollutants, no covariates), adjusted single-pollutant models (pollutant + covariates, no co-pollutants), and adjusted multi-pollutant models (all pollutants + covariates).

Missingness varied across pollutants and covariates (Figure 1). We performed multiple imputation by chained equations with 40 imputations, including all pollutants, covariates, and outcomes as predictors (outcomes not imputed). Diagnostic checks confirmed stable convergence, plausible distributions, and negligible Monte Carlo error relative to standard errors. For the primary analytic sample, we restricted analyses to MSA-year observations in which 4 or more pollutant values (K4) were available for predictor variables to calculate imputed values, and no more than 2 pollutants were missing for a given MSA-year. Sensitivity analyses using K5 and K6 thresholds yielded similar estimates and consistent findings (Figure S2).

Additive interactions were assessed following a validated approach [30]. To assess departure from additivity, we dichotomized each pollutant at its MSA-year median (high vs low) and, for each pair, fit adjusted mixed-effects negative binomial models with the four joint-exposure cells (A^-B^- reference, A^+B^-, A^-B^+, A^+B^+). According to Lash et al. [31], additive interactions of relative

Table 1. Summary of study population.

	Median (IQR)	Mean (95% CI)
Demographics		
Mean Age (year)	45.9 (44.9-46.8)	45.9 (45.9-46.0)
Male (% visits)	37.1 (35.6-38.8)	37.2 (37.1-37.3)
Diagnosis Visits		
CRS-OV [+]	152 (99-248)	223 (215-231)
Asthma-OV	284 (208-426)	374 (366-382)
Area-level Estimates*		
Fair/poor Health (%)	16.0 (13.4-19.0)	16.4 (16.3-16.5)
Obesity (%)	29.4 (26.9-32.0)	29.2 (29.1-29.4)
Smoking (%)	19.1 (16.1-22.4)	19.3 (19.1-19.4)
Premature Death (years)[D]	7423 (6247-8612)	7510 (7460-7562)
Low Birthweight (%)	7.80 (6.86-8.75)	7.90 (7.86-7.95)
Social Deprivation Index	41 (26-57)	43 (43-44)
Pollutant Aggregate Level		
Mean $PM_{2.5}$ ($\mu g/m^3$)	8.70 (7.32-10.36)	8.89 (8.81-8.97)
Mean PM_{10} ($\mu g/m^3$)	18.49 (15.23-22.10)	19.58 (19.31-19.86)
8h Max O_3 (ppb)	40.77 (37.63-44.39)	41.07 (40.90-41.23)
8h Max CO (ppb)	396.0 (295.3-527.6)	432.4 (421.8-442.9)
1h Max SO_2 (ppb)	2.88 (1.33-7.11)	5.16 (4.90-5.43)
1h Max NO_2 (ppb)	17.33 (12.73-22.39)	17.71 (17.33-18.09)

Ecological unit of observation: MSA-year combination. [+] -OV, visits per 1,000 well-check visits. [D] Years of potential life lost before age 75 per 100,000 population (age-adjusted). * Data adapted from County Health Ranking & Roadmaps.

risks can be assessed using relative excess risk due to interaction (RERI) and attributable proportion due to interaction (AP). With A^-B^- level as the reference group, a relative risk was computed for each of the other three levels. Excess Relative Risk (ERR) is "1 – relative risk". According to which, the following formulas were derived based on ERR to calculate the indices:

$$\mathrm{RERI} = \mathrm{ERR}_{A+B+} - \mathrm{ERR}_{A-B+} - \mathrm{ERR}_{A+B-}$$

$$\mathrm{AP} = \frac{\mathrm{RERI}}{\mathrm{RR}_{A+B+}}$$

RERI = 0 and AP = 0 indicate a purely additive effect; RERI > 0 and AP > 0 indicate synergy; RERI < 0 and AP < 0 indicate antagonism.

All statistical analyses were performed using Stata, Version 19. A two-tailed, α=0.05 level was used to determine statistical significance. Given the large sample size, emphasis was placed on effect sizes and 95% confidence intervals [32].

Results

Study population

A summary of the study population is provided in Table 1. Among 5,104 MSA-year observations between 2007–2020, the median CRS-OV was 152 per 1,000 WCs (IQR 99–248), and the median asthma-OV was 284 (IQR 208–426). Premature mortality averaged 7,510 years of potential life lost before age 75 per 100,000 (IQR 6,247-8,612), and median low birthweight prevalence was 7.8% (IQR 6.9–8.8). On average, 16.4% (IQR 13.4-19.0) reported fair/poor health, 29.2% (IQR 26.9-32.0) had obesity, and 19.3% (IQR 16.1–22.4) reported currently smoking. Mean annual pollutant concentrations were: $PM_{2.5}$ 8.9 $\mu g/m^3$ (SD 2.6), PM_{10} 19.6 $\mu g/m^3$ (SD 7.3), O_3 41.1 ppb (SD 4.9), CO 432 ppb (SD 215), SO_2 5.2 ppb (SD 5.7), and NO_2 17.7 ppb (SD 7.1). Histogram distribution of pollutant levels is illustrated in Figure 2.

Associations between pollutants and outpatient visits

Following the imputation approach, 1,926 ecological observations inclusive of 153 unique MSAs were included in the analysis (Figure 1). In single-pollutant adjusted models, higher concentrations of all pollutants were associated with increased CRS-OV and asthma-OV (Figure 3), with effects consistently higher for CRS-OV compared to asthma-OV.

In multi-pollutant adjusted models (Figure 3), only $PM_{2.5}$ and SO_2 remained independently associated with both CRS-OV and asthma-OV. For CRS-OV, the adjusted IRR per SD increase was 1.15 (95% CI, 1.12–1.19) for $PM_{2.5}$ and 1.12 (95% CI, 1.08–1.15) for SO_2. For asthma-OV, the adjusted IRR was 1.06 (95% CI, 1.04–1.09) for $PM_{2.5}$ and 1.10 (95% CI, 1.07–1.13) for SO_2. The dotted versus solid lines in Figure 2 show that the magnitude of association for $PM_{2.5}$ and SO_2 attenuated modestly after co-pollutant adjustment but remained robust, whereas the associations for PM_{10}, O_3, CO, and NO_2 mostly extinguished. Of note, all pollutant levels were not significantly associated with the volume of wellness checkup visits (IRR: $PM_{2.5}$ 1.04 [0.94, 1.16], PM_{10} 1.02 [0.90, 1.16], O_3 0.91 [0.85, 1.00], CO 1.03 [0.96, 1.11], SO_2 0.92 [0.84, 1.02], NO_2 1.09 [0.97, 1.21]).

Additive interaction analyses

Several pollutant pairs demonstrated positive additive interactions (Figure 4). For CRS-OV, the IRR for high $PM_{2.5}$ alone (vs both low) was 1.136 (1.016–1.255) and for high SO_2 alone was 1.018 (0.890–1.146). Under additivity, the expected joint IRR would be 1.154. The observed joint IRR was 1.529 (1.325–1.733), exceeding expectation by 0.375 (RERI 0.375; 95% CI 0.183–0.567). The attributable proportion was 0.245 (95% CI 0.133–0.358), indicating that about one quarter of the combined effect is attributable to interaction.

For asthma-OV, the IRR for high $PM_{2.5}$ alone was 1.087 (0.959–

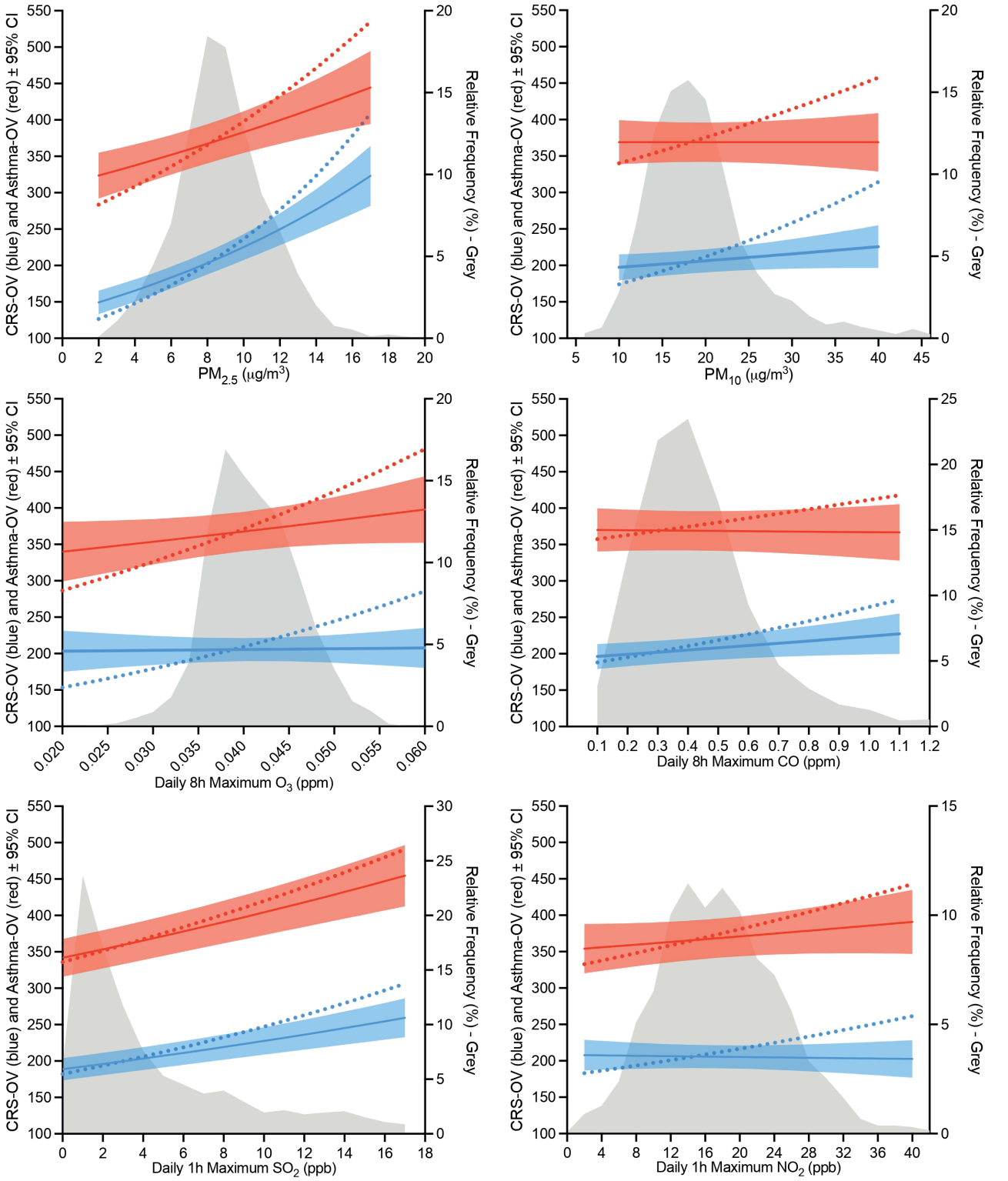

Figure 2. Exposure distributions and adjusted associations of air pollutants with outpatient visits for chronic rhinosinusitis (CRS; blue) and asthma (red). CRS-OV and asthma-OV are normalized by wellness check-ups; y-axis is presented as the number of visits per 1,000 wellness checkups. Gray histograms show MSA-year exposure distributions (right y-axis). Lines are marginal predictions from mixed-effects negative binomial models employing cumulative exposure: dotted = estimates in single-pollutant model; solid with shaded ribbons = estimates and 95% CIs after adjusting for co-pollutant levels. All models adjust for age, sex, SDI, premature mortality, fair/poor health, poor physical-health days, low birthweight, smoking, obesity, and preventable hospitalizations; estimates were pooled across multiple imputations (m=40).

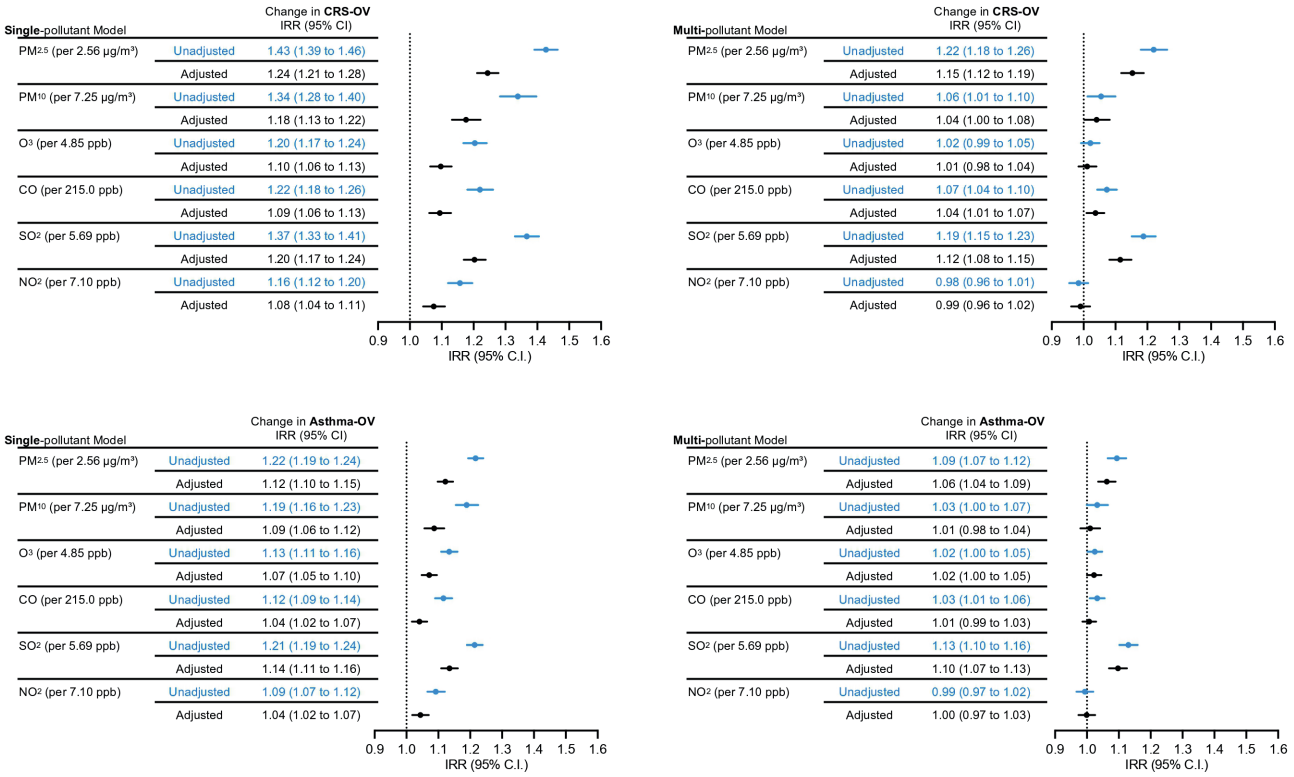

Figure 3. Associations of ambient air pollutant levels with outpatient visits for chronic rhinosinusitis (CRS-OV) and asthma (Asthma-OV). Results are derived from pooled multivariable negative binomial regression models after multiple imputation. Adjusted models include covariates for age, sex, area-level social deprivation index, premature death rate, self-reported health status, low birthweight rate, smoking rate, obesity rate, and preventable hospital visit rate. Single-pollutant models do not account for other pollutants, whereas multi-pollutant models adjust for all co-pollutant levels.

1.215) and for high SO_2 alone was 1.025 (0.901–1.148), implying an expected joint IRR of 1.112. The observed joint IRR was 1.367 (1.179–1.555), yielding RERI 0.255 (95% CI 0.064–0.447) and AP 0.187 (95% CI 0.057–0.317).

The $PM_{2.5} \times NO_2$ pair also showed synergy for asthma-OV. High $PM_{2.5}$ alone had IRR 1.099 (0.968–1.231) and high NO_2 alone had IRR 0.990 (0.865–1.115), giving an expected joint IRR of 1.089. The observed joint IRR was 1.296 (1.083–1.510); thus RERI 0.207 (95% CI 0.022–0.392) and AP 0.160 (95% CI 0.027–0.292).

Discussion

Regulatory frameworks for air quality have historically focused on lower-airway conditions, particularly asthma and COPD, as sentinel endpoints. This emphasis can be traced to landmark epidemiologic studies, including the Harvard Six Cities and American Cancer Society cohorts, which established robust associations between $PM_{2.5}$ and cardiopulmonary morbidity and mortality [3,4]. These findings, reinforced by subsequent work linking $PM_{2.5}$ to hospitalizations and asthma exacerbations, informed the structure of the EPA's Integrated Science Assessments and NAAQS, which continue to rely on lower-airway outcomes as primary indicators of pollution-related health burden [6-8].

In contrast, upper-airway diseases such as CRS have remained largely absent from regulatory science, despite laboratory and clinical evidence that the sinonasal mucosa is highly vulnerable to environmental insult. Studies have demonstrated that particulate exposure disrupts sinonasal epithelial integrity, triggers oxidative stress, and exacerbates sinonasal inflammation [33-37]. Epidemiologic analyses have associated higher levels of PM exposure to increased CRS incidence, severity, and perioperative complications [19,20,38,39]. Results from the present study not only confirm this epidemiological association but also suggest that $PM_{2.5}$ exposure is more strongly associated with CRS outpatient burden than with asthma.

The deposition paradigm posits that coarse particulates (PM_{10}) deposit primarily in the upper airway, while fine particulates ($PM_{2.5}$) have a longer trajectory when inspired, and penetrate deeper into the lower respiratory tract [10]. However, $PM_{2.5}$ emerged as the most consistent predictor of CRS outpatient burden in our analyses, while the associations of PM_{10} were largely attenuated after multi-pollutant adjustment. Our findings align with known pathophysiological characteristics of $PM_{2.5}$ with respect to respiratory health. Fine particulates, unlike coarse particulates, are capable of traversing sinonasal epithelial barriers,

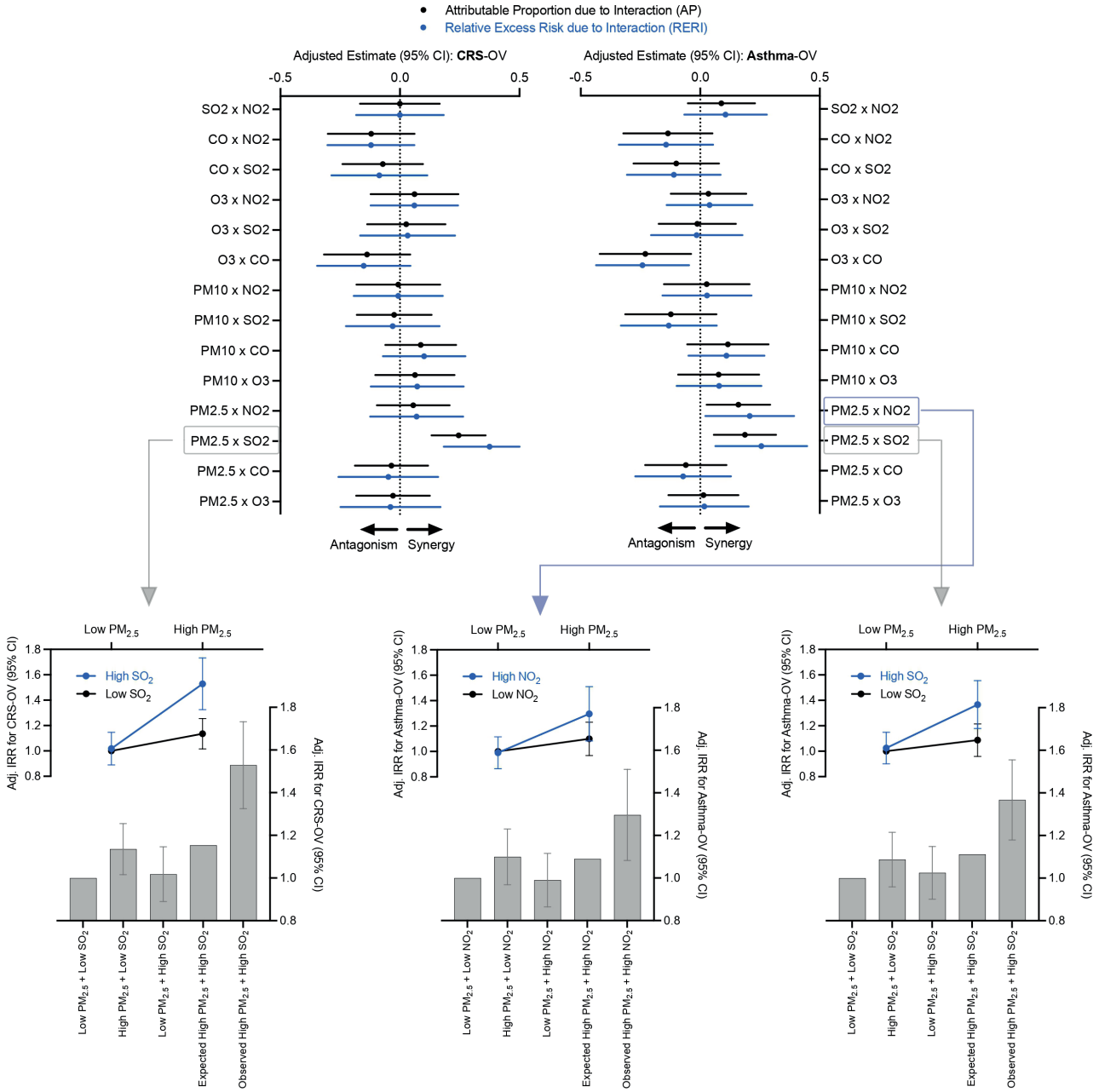

Figure 4. Additive interaction of pollutant pairs on outpatient burden of CRS and Asthma. Top panels illustrate metrics quantifying interaction: attributable proportion due to interaction (AP) and relative excess risk due to interaction (RERI). Positive RERI and AP indicate synergy, negative RERI and AP indicate antagonism. Models adjust for core demographics, community health covariates, and linear co-pollutant levels. Bottom panels depict representative synergistic pairs. The excess of the observed joint risk over the additive expectation corresponds to the RERI, quantifying departure from additivity.

disrupting tight junctions, altering host microbial communities, and generating sustained inflammatory signaling [34,36,37,40]. The sinonasal epithelium, as the primary portal of entry for inhaled pollutants, may represent an earlier or more sensitive site of injury than the distal airway given its constant exposure to inhaled air and extensive epithelial surface area [10]. PM_{10} may act more as a proxy for correlated exposures than as an independent driver of sinonasal disease. Ultimately, data to date suggest that $PM_{2.5}$ exposure is associated with diseases of both the upper and lower airway. Regulatory reliance on lower-airway endpoints alone may underestimate the full spectrum of morbidity attributable to air pollution.

Beyond PM, evidence linking other pollutants to CRS has been more inconsistent. Single-institution studies have associated higher O_3 exposure with increased sinonasal inflammation

and symptom severity, and elevated ambient CO and SO_2 have correlated with poorer outcomes following endoscopic sinus surgery or corticosteroid therapy [41-43]. A 2020 multicenter time-series analysis in China reported increased CRS outpatient visits associated with NO_2, SO_2, and CO but not O_3, and a prospective UK Biobank cohort of over 360,000 participants linked long-term NO_x exposure to higher CRS risk [20,44]. In contrast, population-based studies in Korea and among U.S. veterans found no significant differences in O_3 or NO_2 exposure between CRS and control groups [45].

In our analysis, elevated levels of all six EPA-monitored pollutants were initially associated with increased CRS and asthma outpatient visits, but only $PM_{2.5}$ and SO_2 remained independently associated after adjustment for co-pollutant exposures. As such, much of the apparent association of O_3, NO_2, CO, and PM_{10} reflects covariance with $PM_{2.5}$ and SO_2 rather than direct causal effects. $PM_{2.5}$ has been consistently linked to sinonasal epithelial disruption, oxidative stress, and chronic inflammation [34-37]. SO_2 has received less attention, yet its physiochemical properties offer a compelling rationale for causative associations with inflammatory sinonasal disorders. As a highly soluble irritant gas, SO_2 dissolves in airway surface liquid, injures epithelial barriers, increases mucus secretion, and amplifies oxidative stress responses [46,47]. Higher ambient SO_2 levels have also been associated with less favorable postoperative outcomes following sinus surgery [43]. All in all, while a broad array of pollutants has shown apparent associations with outpatient burden of upper and lower respiratory disease, independent associations are concentrated in $PM_{2.5}$ and SO_2. These exposures may serve as the most reliable indicators of health impact in ambient monitoring data.

When $PM_{2.5}$ and SO_2 were concurrently elevated, the associated rise in outpatient burden exceeded the additive expectation, with nearly one quarter of the joint CRS association and nearly one fifth of the joint asthma association attributable to interaction. $PM_{2.5}$ in combination with NO_2 was also associated with similar synergy for asthma. Previous laboratory experiments have revealed that SO_2 and NO_2 increase epithelial permeability and oxidative stress, potentially facilitating the entry of PM and particulate-induced injury [44,46,47]. Within the sinonasal mucosa, where particulate and gaseous exposures converge, these interactions may intensify inflammation disproportionately.

Since $PM_{2.5}$ and SO_2 emerged as both independent predictors and synergistic amplifiers of CRS and asthma outpatient burden, policies targeting their simultaneous reduction may yield outsized health benefits. The demonstration of pollutant interactions strengthens the case for multipollutant regulatory approaches, long recognized as scientifically necessary but not yet fully implemented [23]. Recognition of synergy in policy would ensure that reductions in one pollutant are valued not only for their direct effects but also for their ability to magnify gains from reductions in others.

The 2019 EPA Integrated Science Assessments for particulate matter and the 2024 EPA technical support document estimating health impacts of $PM_{2.5}$ and ozone reductions continue to emphasize hospitalizations and mortality from cardiopulmonary and lower-airway conditions [7,8]. The California Air Resources Board's 2022 Health Endpoints Bulletin likewise prioritizes asthma, COPD, and cardiovascular outcomes [5]. Since the outpatient burden of CRS exhibits stronger and steeper associations with air pollution than that of asthma, these frameworks may be systematically underestimating the true health burden of air pollution by overlooking its impact on upper airway disease. While differences in management between CRS and asthma may play a role, as asthma care is more guideline-directed and potentially less dependent on visit frequency, the greater sensitivity of CRS-related outpatient demand to pollution remains noteworthy and warrants public health attention.

Although the prevalence of CRS is somewhat lower than asthma, CRS has economic, quality-of-life and clinical burdens on par with asthma. For refractory CRS the cost of lost productivity is ~$10,000 per patient per year [48,49], vs. $10,000 to $12,800 for severe asthma [50-52]. Patients with CRS with nasal polyps have also been shown to have comparable quality of life impairments to asthma, based on SF-36 and EQ-VAS scores [53]. From a clinical standpoint, when CRS and asthma co-exist, each condition can worsen the other's course and compound their quality-of-life impact, well described as the unified airway hypothesis [54-56]. For regulatory science to fully capture the impact of air pollution, CRS should be considered as a sentinel health endpoint alongside asthma.

This study has several limitations. MarketScan includes commercially insured patients ≤65 years, limiting generalizability to uninsured individuals and public insurance enrollees. Diagnoses were derived from administrative coding rather than standardized clinical confirmation. Geographic resolution was restricted to the CBSA level, which, while less granular than county or ZIP code, is widely used by federal agencies for surveillance and regulatory purposes. Importantly, exposure data were derived from the EPA's monitoring network, the same data which underlie national air quality standards and guide policy and regulatory decision-making. Although the EPA network has variable spatial and temporal density, it remains the national gold standard for national air quality surveillance.

Conclusion

Ambient air pollution was associated with increased outpatient burden for both CRS and asthma, with effects that were particularly pronounced for CRS. Adjusting for co-pollutant levels, fine particulate matter and sulfur dioxide emerged as independent and synergistic predictors of outpatient volume. CRS should be recognized alongside asthma as a pollution-sensitive disease and incorporated into regulatory health assessments. Policies prioritizing simultaneous reductions in $PM_{2.5}$ and SO_2 and adopting multipollutant approaches may yield outsized health benefits, more accurately capturing the true impact of air quality on upper and lower respiratory disease.

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Author contributions

HHY conceived and designed the study, performed the statistical analysis, interpreted the data, drafted the initial manuscript, revised it critically, and approved the final version. EV contributed substantially to the study design, critically revised the manuscript, and approved the final version. PH contributed significantly to the study conception, study design, interpretation of results, and approved the final version.

Conflict of interest

Hong-Ho Yang and. Esther Velasquez have no conflict of interest to disclose. Peter Hwang is a consultant for Medtronic, ClaraSim; Equity ownership for SoundHealth; all relationships are of minimal relevance to this study.

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Peter H. Hwang, MD
Professor and Vice Chair
Department of Otolaryngology
Head & Neck Surgery
Chief, Division of Rhinology &
Endoscopic Skull Base Surgery
Stanford University School of
Medicine
801 Welch Road
Stanford, CA 94305
USA

Tel: +1 (650) 736-3223
Fax: +1 (650) 723-5893
E-mail: hwangph@stanford.edu

Hong-Ho Yang[1], Esther Velasquez[2], Peter H. Hwang[1]

[1] Department of Otolaryngology - Head and Neck Surgery, Stanford University School of Medicine, Stanford, CA, USA

[2] Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA, USA

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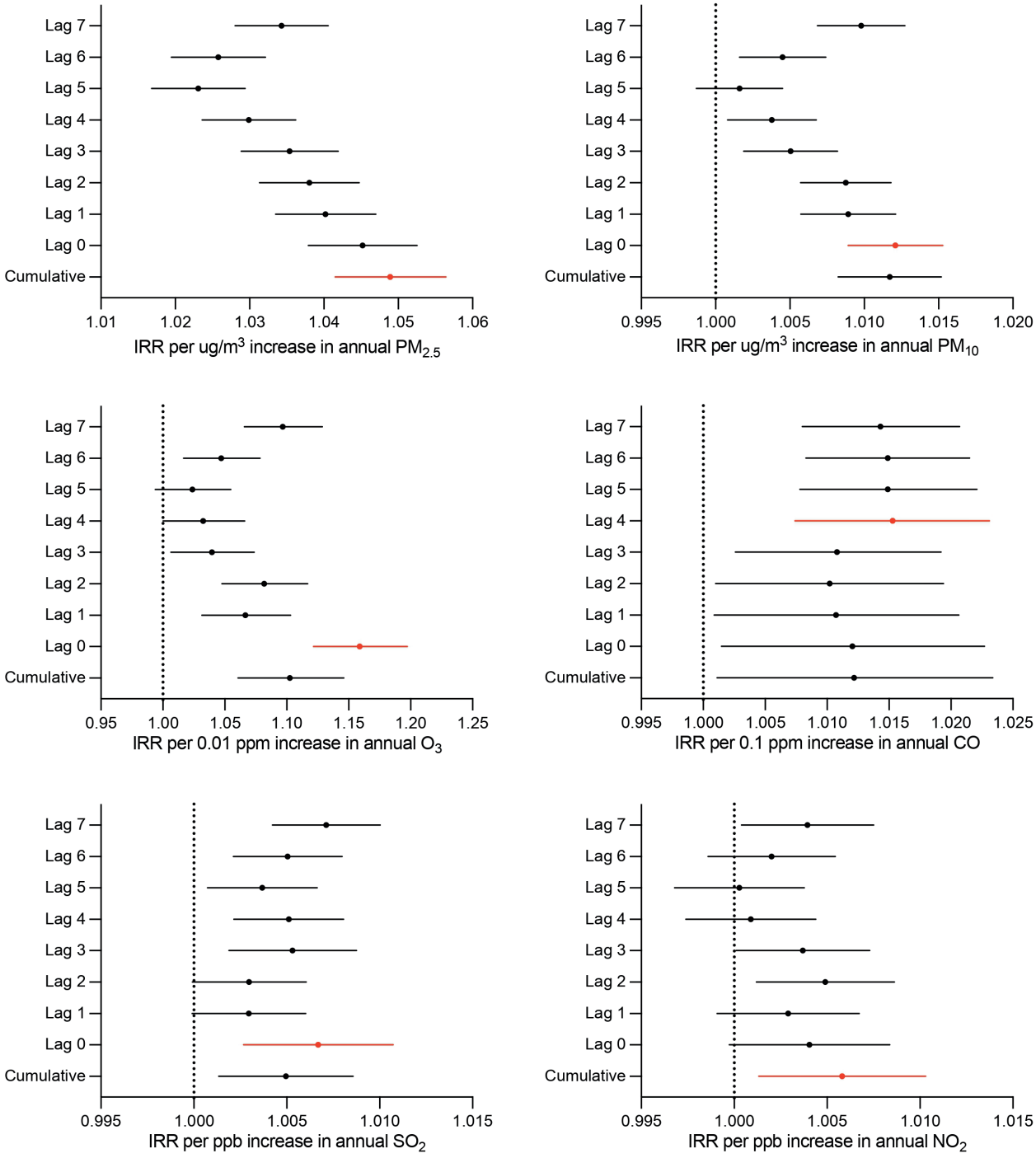

Figure S1. Lag sensitivity analyses. Lag-specific and cumulative associations of pollutant exposures with CRS-OV across 0–7 years. Red indicates model with the largest effect size.

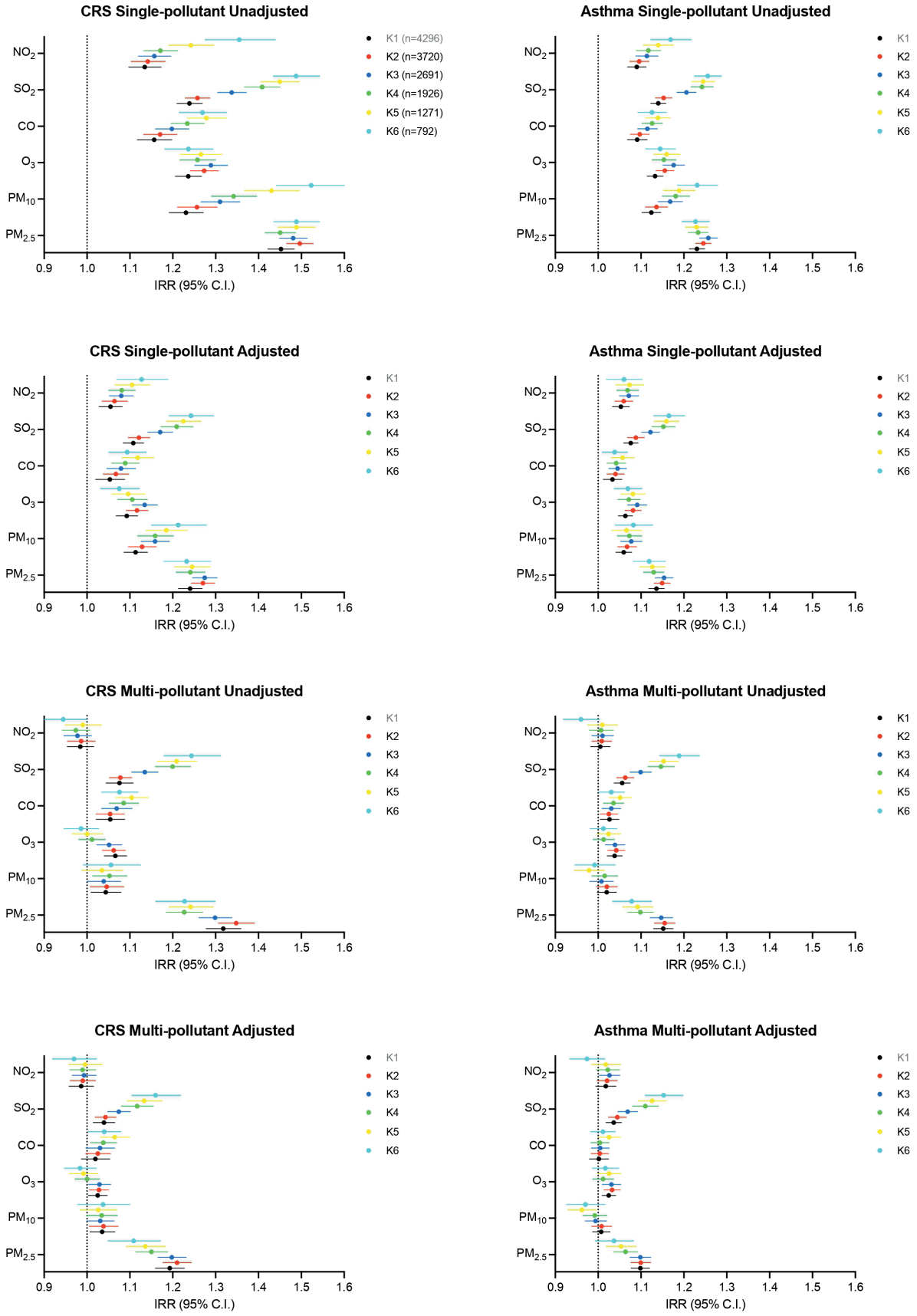

Figure S2. Imputation sensitivity analyses. Associations of pollutant exposures with CRS-OV and asthma-OV across imputation sets K1–K6. K1 includes MSA-year observations with ≥1 pollutant available; K2 with ≥2; K3 with ≥3; K4 with ≥4 (primary analysis); K5 with ≥5; and K6 with all 6 pollutants observed. Results are shown for single- and multipollutant models, unadjusted and adjusted, to assess robustness to missingness.